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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/674,292	08/01/2001	Andrew P. McMahon	21508-022 Nat	5115

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EXAMINER	
NICHOLS, CHRISTOPHER J	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 06/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/674,292	MCMAHON ET AL.	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Applicant's election **without** traverse of Group I (claims 1-9) drawn to an enriched population of mammalian neural precursor cells and an enriched population of mammalian dopaminergic neuron precursor cells in Paper No. 16 (7 April 2003) is acknowledged.

Status of Application, Amendments, and/or Claims

2. The Preliminary Amendment filed 7 April 2003 (Paper No. 16) has been received and entered in full. Claims 10-20 have been cancelled, claim 21 has been added, and claim 6 has been amended.

Oath/Declaration

3. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

> The oath or declaration is defective because: Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

Specification

4. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

5. Applicant is reminded of the proper language and format for an abstract of the disclosure.

6. The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

7. The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

8. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

Claim Objections

9. Claim **2** is objected to because of the following informalities: "characaterized" is misspelled. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims **1-9** and **21** are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described

in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

11. The above invention is drawn to an enriched population of mammalian neural precursor or dopaminergic neuron precursor cells said cells being characterized in that they exhibit a stem cell phenotype in the presence of a Wnt polypeptide and differentiate into dopaminergic neurons in the absence of said Wnt polypeptide. The language of said claims encompasses Wnt polypeptides including Wnt-1, Wnt-2, Wnt-3a, Wnt-7a, and Wnt-7b.

12. The Specification teaches that Wnt polypeptides are secreted cysteine-rich glycosylated polypeptides that play a role in the development of a wide range of organisms including embryonic induction, generation of cell polarity, and the determination of cell fate. The Specification also details the role of signaling molecules, Wnt knockout mice, in regards to embryonic development. No evidence is presented to fairly demonstrate possession of the claimed cell lines at the time of invention.

13. The specification as filed does not provide any guidance or examples that would enable a skilled artisan to make the claimed enriched cell populations. Additionally, a person skilled in the art would recognize that predicting the efficacy of using a specific polypeptide based solely embryonic expression patterns as highly problematic. Thus, although the specification prophetically considers and discloses general methodologies of making the enriched cell populations, such a disclosure would not be considered enabling since the state of stem cells and Wnt polypeptides is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;

(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

14. The following references are cited herein to illustrate the state of the art of Wnt polypeptides and their activity.

15. Concerning the breadth of the claims, Kispert *et al.* (20 September 1998) "Wnt-4 is a mesenchymal signal for epithelial transformation of metanephric mesenchyme in the developing kidney." Development **125**: 4225-4234 teaches that Wnt-4 is required for tubule formation, is sufficient to trigger tubulogenesis, and is essential for kidney development (pp. 4225, 4232). Also concerning the breadth of the claims, Miller and Sassoon (21 July 1998) "Wnt-7a maintains appropriate uterine patterning during the development of the mouse female reproductive tract." Development **125**: 3201-3211 teach that Wnt genes are primarily restricted to either mammary stroma or epithelium and that Wnt-7a, in particular, is expressed in the female mammalian reproductive tract (pp. 3201-3202). Thus Miller and Sassoon teach a role for Wnt-7a that is contrary to the instant invention (Figure 9). Willert *et al.* (22 May 2003) "Wnt proteins are lipid-modified and can act as stem cell growth factors." Nature **423**: 448-452 demonstrated that Wnt-3a acts as a growth factor for hematopoietic stem cells (HSCs) (Figure 3). This reference does not support the limitations of the claims requiring Wnt-3a, Wnt-4, and Wnt-7a to stimulate neuronal stem cell proliferation and differentiation upon withdrawal thereof.

16. In regards to the nature of the invention, US 6159462 (12 December 2000) Matthews & Austin teaches that Wnt polypeptides are used to enhance or increase myelopoiesis,

erythropoiesis or lymphopoiesis in $CD34^{+}$, $AA4^{+}$, and/or flASK cells (claims 1-5). In view of the nature of the invention, US 5851984 (22 December 1998) Matthews & Austin. US 6159462 teaches that Wnt can be used to stimulate proliferation and differentiation in hematopoietic stem or progenitor cells (claims 1-20). In further view of the nature of the invention, US 6485972 B1 (26 November 2002) McMahon *et al.* US 6485972 teaches that Wnt polypeptides can be used to stimulate maturation of an immature oocyte (claims 1-3). The instant invention runs contrary to these references.

17. On the state of the prior art, Austin *et al.* (15 May 1997) "A Role for the Wnt Gene Family in Hematopoiesis: Expansion of Multilineage Progenitor Cells." Blood **89**(10): 3624-3635 Wnt-1, Wnt-5a, and Wnt10b exert a growth factor effect on HSCs (Figure 2). Bradley and Brown (August 1995) "A Soluble Form of Wnt-1 Protein with Mitogenic Activity on Mammary Epithelial Cells." Molecular and Cellular Biology **15**(8): 4616-4622 demonstrate that Wnt-1, present in condition medium, have no effect on fibroblasts (pp. 4617). Wnt-1, however, exerts a mitogenic effect on C57MG and RAC311 cells (mammary epithelial cell lines) (Figures 1-7).

18. Taken into consideration, the references above would teach a skilled artisan that Wnt polypeptides could be expected to exert mitogenic effects on HSCs. No teaches lead the skilled artisan to predict or expect that Wnt polypeptides would have the claimed effect on neural stem cells.

19. Regarding derivatives and fragments of SEQ ID NO: 1, the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. For instance, Echelard *et al.* (1994) "Cis-acting regulatory sequences governing Wnt-1 expression in the developing mouse CNS."

Development **120**: 2213-2224 teaches that Wnt-1 is a protooncogene (Abstract). Thus mutations and variants of Wnt-1 may lead to tumor development (see Stedman's Medical Dictionary). While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions [see Wells (18 September 1990) "Additivity of Mutational Effects in Proteins." Biochemistry **29**(37): 8509-8517; Ngo *et al.* (2 March 1995) "The Protein Folding Problem and Tertiary Structure Prediction, Chapter 14: Computational Complexity Protein Structure Prediction, and the Levinthal Paradox" pp. 492-495]. In addition, Mason *et al.* (May 1992) "Mutational Analysis of Mouse Wnt-1 Identifies Two Temperature-Sensitive Alleles and Attributes of Wnt-1 Protein Essential for Transformation of a Mammary Cell Line." Molecular Biology of the Cell **3**(5): 521-533 teaches that mutations have varying effects on Wnt-1 (Tables 1-3 and Figures 3-5). Thus a skilled artisan is confronted with an undue burden of experimentation to determine which mutations, deletions, and substitutions, are tolerable such that they still allow for the manufacture of the claimed enriched cell population.

20. In this regard, the Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by

amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone [Bork (2000) "Powers and Pitfalls in Sequence Analysis: The 70% Hurdle." Genome Research **10**:398-400; Skolnick and Fetrow (2000) "From gene to protein structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39, especially p. 36 at Box 2; Doerks *et al.*, (June 1998) "Protein annotation: detective work for function prediction." Trends in Genetics **14**(6): 248-250; Smith and Zhang (November 1997) "The challenges of genome sequence annotation or 'The devil is in the details'." Nature Biotechnology **15**:1222-1223; Brenner (April 1999) "Errors in genome annotation." Trends in Genetics **15**(4): 132-133; Bork and Bairoch (October 1996) "Go hunting in sequence databases but watch out for the traps." Trends in Genetics **12**(10): 425-427].

21. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of isolating the claimed cell lines as exemplified in the references above.

22. The instant claims are drawn very broadly to human and porcine precursor cell lines, including fetal cell lines which maintain a stem cell phenotype in the presence of a Wnt polypeptide and then differentiate, preferably into dopaminergic neurons, upon withdrawal of said Wnt polypeptide. Since the specification fails to provide any guidance for the successful isolation and enrichment of said cell population, and since resolution of the various complications in regards to the culturing and characterization of stem cells is highly unpredictable, one of skill in the art would have been unable to make the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the prior art as outlined below, the quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of formulations with known Wnt polypeptides and stem cell lines to correlate the presence or absence of Wnt polypeptides to the cell populations state of differentiation. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

Summary

23. Claims 1-9 and 21 are hereby rejected.

24. The following art was found by the Examiner during the art search and is here made of note:

a. CA 2200794 (28 September 1998) Fraser and St. George-Hyslop (discloses polypeptide with 100% sequence homology to SEQ ID NO: 1).

b. Ooyen *et al.* (1985) "The nucleotide sequence of human int-1 mammary oncogene; evolutionary conservation of coding and non-coding sequences." The EMBO Journal **4**(11): 2905-2909 (discloses a polypeptide with 100% homology to SEQ ID NO: 1).

c. Burrus and McMahon (October 1995) "Biochemical Analysis of Murine Wnt Proteins Reveals both Shared and Distinct Properties." Experimental Cell Research **220**(2): 363-373.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:00AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

CJN
June 24, 2003

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:00AM to 5:00PM.

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Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Elizabeth C Kemmerer

CJN
June 20, 2003

ELIZABETH KEMMERER
PRIMARY EXAMINER